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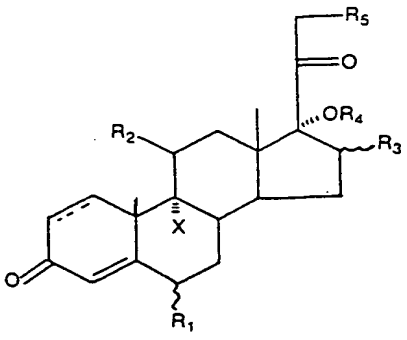
(54) Steroidal esters and process for the preparation of steroidal esters.

(57) A process for the preparation of corticosteroid esters of the formula



(I)

wherein
--- signifies that a double bond can be present;
X is hydrogen, fluorine or chlorine;
R_1 is hydrogen, fluorine, chlorine or methyl, which may be either α or β;
R_2 is halogen, oxo, i.e. ketonic oxygen, or hydroxyl;
R_3 is hydrogen, α-methyl or β-methyl;
R_4 is an acyl group of the formula RCO, in which R is one of the following:
i) an alkyl group containing 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;
ii) an aralkyl group of 7 to 8 carbon atoms; or
iii) a phenyl group;
R_5 is hydroxyl or R_6; where
R_6 is hydrogen, halogen, two halogen atom substituents or OR_7, where R_7 is an acyl group of the formula R'CO in which R', which can be identical or different to R in the same molecule, is one of the following:
i) an alkyl group containing 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;
ii) an aralkyl group of 7 to 8 carbon atoms; or
iii) a phenyl group;
which comprises esterifying a compound of the formula

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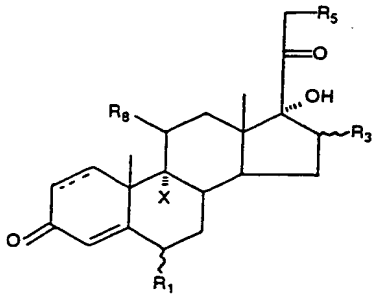
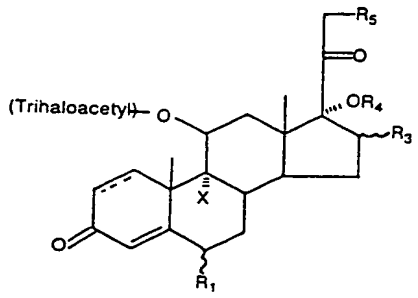


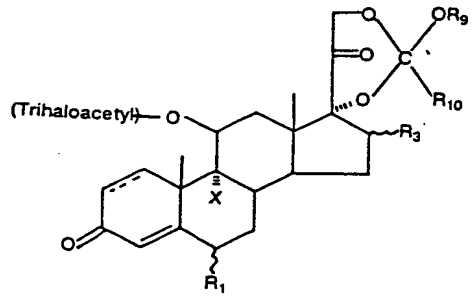
(III)

wherein X, R_1, R_3 and R_5 are as defined above, and
R_8 is trihaloacetate, halogen or oxo;
at the 17- position only, or at the 17- and 21- positions when R_5, in formula III, is hydroxyl, the said esterification being carried out with the anhydride of the acid containing the group it is desired to enter at the 17- position, or at the 17- and 21- positions, together with a pair of strong acids; and if desired eliminating immediately thereafter any 11-trihaloacetate substituent, to form a compound of formula I, wherein R_2 is hydroxyl, R_5 is R_6, and X, R_1, R_3 and R_4 are as defined above; or when R_8 is halogen or oxo and R_5 is R_6, isolating a compound of formula I after the said esterification; or treating a compound of formula IV from the esterification



(IV)

wherein R_5 is R_6, by eliminating the 11-trihaloacetate group therefrom by reaction, in the presence of a lower alcohol, with an organic amine (other than one in which the nitrogen forms part of an aromatic ring), or ammonia gas dissolved in a suitable anhydrous solvent, or ammonium hydroxide or hydrazine, to produce a compound of formula I wherein R_2 is hydroxyl, R_5 is R_6 and X, R_1, R_3 and R_4 are as defined from formula I; or by so eliminating the 11-trihaloacetate group from a compound of formula



(V)

wherein X, R_1 and R_3 are as defined for formula I;
R_9 is an alkyl group of 1 to 3 carbon atoms; and
R_{10} is a hydrocarbon group comprising one of the following:
i) an alkyl group of 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;
ii) an aralkyl group of 7 to 8 carbon atoms; or
iii) a phenyl group;
to form a compound of formula I, wherein R_2 and R_5 are both hydroxyls, and R_1, R_3, R_4 and X are as defined for formula I.

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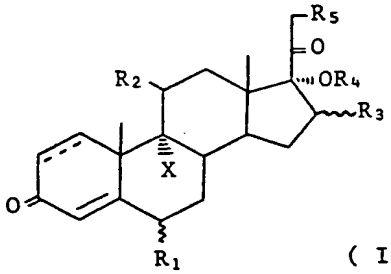
STEROIDAL ESTERS AND PROCESS FOR THE PREPARATION OF STEROIDAL ESTERS

This invention relates to a process for the preparation of steroidal esters, and to certain of such steroidal esters, which are novel per se.

Corticosteroids have long been known for their anti-inflammatory activity. It has been similarly known that the topical activity can be considerably enhanced by the introduction of ester functions, especially at the 17- position only and at the 17- and 21- positions. These esterified corticosteroids also offer the advantage of minimal systemic activity.

The present invention provides a new and efficient route to compounds of the following formulae



(I)

in which

---- signifies that a double bond can be present;

X is hydrogen, chlorine or fluorine;

R_1 is hydrogen, fluorine, chlorine or methyl, which may be either α or β;

R_2 is halogen, oxo or hydroxyl;

R_3 is hydrogen, α-methyl or β-methyl;

R_4 is an acyl group of the formula RCO, in which R is one of the following

i) an alkyl group containing 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;

ii) an aralkyl group of 7 to 8 carbon atoms;

iii) a phenyl group;

R_5 is hydroxyl or R_6; where

R_6 is hydrogen, one or two halogen atom substituents or OR_7, where R_7 is an acyl group of the formula R'CO in which R', which can be identical or different to R in the same molecule, is one of the following

.../...

i) an alkyl group of 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;

ii) an aralkyl group of 7 to 8 carbon atoms; or

iii) a phenyl group.

Thus, the present invention covers the preparation of betamethasone, dexamethasone, beclomethasone, clobetasol, prednisolone, hydrocortisone esters by one general process.

The known prior art processes available for the preparation of such compounds can be split into three groups.

The first is the direct introduction of 17- ester function, without any protection at, for instance, the 11- position. This was exemplified by Huang-Minlon et al. in J. Amer. Chem. Soc. 74, 5394-96, (1952) and in British Patents 737.291 (priority 1952) and 1.070.751 (priority 1964), and U.S. Patent 3.721.687 (priority 1970). The acylation was carried out with the anhydride of a lower aliphatic carboxylic acid, in the presence of a strong acid catalyst, such as p-toluenesulphonic acid.

It is well known that the order of esterification of hydroxyl functions is primary hydroxyls, then secondary and finally tertiary. Thus, in the case of an 11,17,21-trihydroxy steroid, direct esterification will give a mixture made up of some varying percentages of the 21-monoester, 11,21-diester and 11,17,21-triester. The separation of the required product is normally not economically feasible, even if a suitable process can be found. Additionally, no method for the selective removal of an unactivated 11-ester in an 11,17,21-triester is at present known.

The second methodology covers the use of functional group protection prior to the introduction of the ester function(s). The usual protecting groups for the 11-hydroxyl function were the trihaloacetate, the trimethylsilyl ether, the tetrahydropyran-(2'yl)ether, and the nitrate ester. The first of these was initially described by Reichstein in U.S. Patent 2.800.489 (priority 1953), and has been used in British Patent 1.097.165 (priority 1965) and U.S. Patent 4.024.131 (priorities 1974 and 1975). The trimethylsilyl ether was used in British Patent 1.227.992 (priority 1968), wherein the preparative method involved extraction techniques, which are in preference to be avoided, whilst the yields given are not particularly good. The tetrahydropyran-(2'yl)ether group was described in U.S. Patent 4.024.131 and similarly the preparative method involved extraction techniques. Nitrate ester protection was first described in British Patent 1.082.573 (priority

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1965) and then again in British Patent 1.158.492 (priority 1966). In the latter disclosure it was stated that the technique was not universally applicable, especially for 21-desoxy steroids, due to the formation of the 17-nitrate ester.

Once the 11-hydroxyl group and any other sensitive groups have been protected, the 17-acylation is carried out. The first process to be used was that given in British Patent 737.291, using the anhydride of a lower carboxylic anhydride in the presence of a strong acid catalyst, such as p-toluenesulphonic acid. This process was further used in British Patents 1.158.492 and 1.227.992, amongst many others. Unfortunately, the process suffers from the disadvantage that it is necessary "to carry out the acylation by heating the 17α-hydroxy-20-keto steroid with the anhydride at temperatures in excess of 100°C for extended periods of time". This causes extensive degradation, especially in steroids containing many sensitive functional groups.

Hence, this process was superseded by the use of an aliphatic or cycloaliphatic carboxylic acid together with trifluoroacetic anhydride, as described in German Patent 1.013.284 (priority 1956), and used in British Patents 1.391.712 (priority 1971) and 1.158.492 and 1.227.992 amongst others. However, this method was only a slight improvement over the then prior art, since it was still necessary to heat the reaction mixture, this time to between 80°C and 90°C.

British Patent 1.097.165 (priority 1965) then described a process which is basically a combination of the two given above in that an aliphatic or cycloaliphatic carboxylic acid containing from one to nine carbon atoms, plus trifluoroacetic anhydride and a strong acid catalyst, such as p-toluene sulphonic acid, are used to effect the desired acylation. It was claimed that this mixture worked at room temperature, making it more applicable than the then prior art. Unfortunately, the quantity of reagents necessary was extremely high, typically ten milliliters of the acid and four milliliters of trifluoroacetic anhydride per gram of the starting steroid. This not only made the process expensive, but it then became difficult to isolate the desired product in a pure state. Hence, the mixtures had to be steam-distilled to remove the vast excess of the acids and then column chromatography was normally used to isolated the products.

After the 17-acylation step it is then necessary to selectively remove the 11- protecting group. A trifluoroacetate group can be removed by solvolysis with silica, as described in British Patent 1.391.712 and in U.S. Pa

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tent 4.024.131; by sodium bicarbonate hydrolysis, as described in U.S. Patent 4.024.131; by solvolysis with an alkali or alkaline earth metal salt of an acid with a pKa of between 2.3 and 7.3, as described in British Patent 1.097.164 (priority 1965); or by catalytic quantities of sodium methoxide, as described in Portuguese Patent 71.309. The tetrahydropyran-(2'yl)-ether and the trimethylsilyl ether protecting groups can be removed by acid hydrolysis, whilst the 11-nitrate ester requires zinc in acetic acid.

In respect of the trifluoroacetate group removal, the use of silica or of an alkali or alkaline earth metal salt of an acid with a pKa value of between 2.3 and 7.3, are not methods of choice. This is due to the heterogeneity of the reaction, resulting in a tendency to leave unreacted starting material in the product and thus giving variable results. This problem can also be obtained when sodium bicarbonate is used, since the product and the starting steroid often co-crystallise in the methanolic medium. The use of catalytic quantities of sodium methoxide is the best available prior art method, but here the reaction parameters must be strictly controlled, otherwise ester functions, especially those at the 21-position, can be removed. This is demonstrated in British Patent 1.196.683 (priority 1967) wherein sodium methoxide removes not only an 11-chlorodifluoroacetyl group, but also a 21-acetate group as well.

The other protecting groups present problems in the preparation of derivatives, eliminating them as candidates for viable processes.

The final general method for the preparation of the compounds of the present invention is via the cyclic 17α,21-orthodiesters. This was first described in Belgian Patents 618.831 and 619.180 (priorities 1962), and then later described in British Patents 1.043.347 and 1.047.518 (priorities 1964). This process, which is only applicable if the starting material has a 17α,21-dihydroxy-20-one sub-structure, works well without the necessity for protection of the 11-hydroxyl. Unfortunately, the acid hydrolysis of the intermediate cyclic orthodiester is not sufficiently selective and is very sensitive to the reaction conditions, yielding in addition to the 17-monoester, the 21-monoester and the 17,21-dihydroxy compounds. Another restraint upon this method is the difficulty of preparation of the starting trialkylorthoesters, those derived from acids with more than six carbon atoms being exceptionally difficult to obtain.

The present invention is based upon the discoveries that the 17-acylation stage can be carried out more simply, more economically in terms of re

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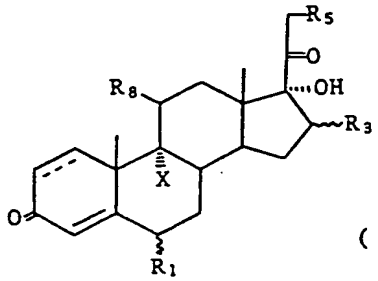
agents, in better yield and purity than has been hitherto the case, and that the removal of a 11-trifluoroacetate protecting group can be most simply accomplished in almost stoichiometric yield by reaction with either an amine, ammonia or hydrazine.

According to the present invention the starting material, which can be prepared by standard methods known to those skilled in the art, is



(III)

in which R_8 is trihaloacetate, oxo or halogen. In the case where R_8 is trihaloacetate, which is by preference the trifluoroacetate, this protecting group is introduced by standard methods, such as dissolving the 11-hydroxy steroid in pyridine, which can be diluted with a solvent inert in the reaction, such as tetrahydrofuran, and adding trifluoroacetic anhydride, and then isolating the required product by conventional means, such as precipitation in water.

The acylation at the 17- position is carried out with the anhydride of the carboxylic acid, plus a pair of strong acids. The quantity of the anhydride which should be used, is from 1.5 moles per mole of starting steroid upwards. Thus, in the case of the introduction of the 17-valerate group into betamethasone 11-trifluoroacetate 21-acetate (Example 9a), the preferred quantity of valeric anhydride is 0.76 ml/gm. This compares very favourably with the conditions given in British Patent 1.097.165, Example 4, of 10 ml of valeric acid per gm of starting material. One of the pair of strong acids should be a trihaloacetic acid, of which trifluoroacetic acid or trichloroacetic acid are preferred. This acid should also be present in molar quantities above 1.5 in comparison with the starting steroid. Again, in the case of the introduction of the 17-valerate group into betamethasone 11-trifluoroacetate 21-acetate, the preferred quantity of trifluoroacetic acid is 0.58ml /gm. In comparison, the above mentioned Example 4 in British Patent 1.097.165 uses 4 ml of trifluoroacetic anhydride per gm of starting material.

The second acid of the pair is present in catalytic quantities and can be chosen from a variety of strong acids. Typical of this choice is p-

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toluenesulphonic acid, methanesulphonic acid, benzenesulphonic acid, perchloric acid, hydrochloric acid.

The order of mixing of the various reagents is not of importance, although it is preferable to cool the reaction vessel during the actual mixing process. Normally, the trihaloacetic acid is cooled to about 0°C, when the acid anhydride is added, followed by the second acid and finally the steroid which is to be reacted.

One of the most surprising features of the present invention, which comprises part of its inventive merit, is that for equivalent quantities of reagents this new process is considerably faster than that given in the prior art.

The following table refers to the introduction of the 17-valerate into Betamethasone 11-trifluoroacetate 21-acetate (See Example 1).

TABLE I

Method	MTFAA/MSS	MTFA/MSS	MVA/MSS	MAVA/MSS	Reaction Temperature	Time to completion by chromatography
British Patent 1.097.165 Example 4	14.84	-	47.44	-	28°C	1 hour
Half of above conditions	7.42	-	23.72	-	28°C	3 hours
Present Invention	-	7.61	-	3.80	28°C	Less than 1 hour
Present Invention	-	4.00	-	2.00	28°C	1 hour

where

$MTFAA/_{MSS}$ is the molar ratio of trifluoroacetic anhydride to the starting steroid

$MTFA/_{MSS}$ is the molar ratio of trifluoroacetic acid to the starting ste

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roid.

$MVA/_{MSS}$ is the molar ratio of valeric acid to the starting steroid.

$MAVA/_{MSS}$ is the molar ratio of valeric anhydride t the starting material.

This increase in the rate of reaction is believed to be due, in part, to the higher dielectric constant of the reaction mixture. This is bourne out by the fact that the use of some inert diluents of relatively low dielectric constant do not allow the reaction to proceed.

Hence, it has been found that esterification occurs in the presence of acetonitrile or nitromethane, whereas in the presence of tetrahydrofuran, dioxan, chloroform and acetone the reaction is extremely slow and even after a 6 hour reaction the majority of the starting steroid is recovered unchanged. It will be noted that the two above mentioned successful diluents have high dielectric constants.

It will be noted that R_5, in the starting material, compound III, can be hydroxyl, so that when symmetrical 17,21-diesters are required, the aforementioned reaction can be carried out on a 17,21-dihydroxy steroid. Once the reaction is complete, the isolation method is dependent upon the starting material and on the desired product. Thus, when R_8 in compound III is oxo or halogen, the product is obtained by conventional means, such as precipitation in water. This is also a part of the inventive merit of the present invention over the prior art, since the latter teaches that steam distillation is usually required. This is to remove the vast excess of reagents originally used, otherwise precipitation yields an oil, which is often intractable. Thus, the minimal quantities desirable in the present invention not only produce a faster, cleaner reaction, but also facilitate the obtention of the required product. Similarly, when R_8 is trihaloacetate, isolation of the product by conventional means, such as precipitation in water, will give the 11-trihaloacetate 17- esterified product. Since the trifluoroacetate group is not pharmaceutically acceptable, it must normally be removed. Thus, a further feature of the present invention is the direct isolation of the 11-hydroxyl compounds, which can be accomplished by the use of amines or ammonia. It has been established that an amine or ammonia, whether in the presence of water or not, will selectively remove an 11-trifluoroacetate group and this will be more fully discussed hereinafter. The substitution pattern of the amine does not seem to be of vital importance. However, those amines in which the nitrogen forms part of an aromatic ring, for example pyridine, are

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inactive and are excluded from the group of useful amines.

It is possible to isolate the required products by two slightly different processes. Thus, the amine can be added to the acylating reaction mixture and the product isolated by conventional means such as precipitation in water. Alternatively, the reaction mixture can be precipitated directly using a water/amine mixture, or using an ammonium hydroxide solution. The quantity of amine or ammonium hydroxide used should be in excess, guaranteeing the neutralisation of the various acidic or pro-acidic constituents of the acylating mixture. In some instances, it is necessary to add, on solubility grounds, an inert diluent, such as dioxan, tetrahydrofuran or dimethylformamide, to ensure that the trifluoroacetate group is completely eliminated. The present invention thus allows the introduction of the ester group(s) required and the subsequent selective removal of the trifluoroacetate protecting group without isolating the intermediate compound, the accomplishment of which has until now required two separate reactions.

The direct precipitation of an 11-trifluoroacetyl 17- esterified steroid was discussed above, and in order to obtain the 11-hydroxyl product, it is necessary to remove the trifluoroacetate group. It has been found that the use of an amine, ammonia or hydrazine, whether in the presence of water or not, can accomplish this in almost stoichiometric yield. The steroid is dissolved in a lower alcohol, preferably methanol or ethanol, plus an inert diluent, such as tetrahydrofuran, dioxan, dimethylformamide, if so required. The amine is then added in small quantities, preferably between 0.01 and 1.0 moles per mole of the starting material. The reaction is normally complete in about fifteen minutes at room temperature. The product can be isolated by conventional means, such as precipitation in water. Alternatively, a solution of ammonia gas in an absolute lower alcohol can be used instead of the amine.

The use of hydrazine is limited to those compounds in which R_5 of formula I is hydrogen, halogen or two halogen substituents. Apart from this, the reaction proceeds in the same manner as for the amines.

Hydrazine is less applicable than amines or ammonia in the case where R_5 in formula I is an acyl group, occasionally provoking the formation of by-products.

As is well known to those skilled in the art, corticosteroid 17-monoesters are particularly active. It is a further inventive feature of the present process that the 11-trifluoroacetate group can be removed from the 11-

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trifluoroacetyl-17-ester-21-hydroxy steroids, utilizing an amine or ammonia. The trifluoroacetate group surprisingly exerts a stabilising effect on the 17-ester function, in that none or negligible quantities of the 21-ester are obtained during the removal of the trifluoroacetate group, it being well known that this transesterification reaction is facile under both acidic or basic conditions. These 11,17-diesters can be best prepared from compound III in which R_5 is either OR_7 or hydroxyl by the above processes of acylation, followed by strong acid solvolysis, as is fully discussed in Portuguese Patent 71.309.

Another example of the surprising stabilising effect of the 11-trifluoroacetate group on the 17-ester function is that the 11-trifluoroacetyl-17α,21-orthodiesters can be successfully hydrolysed in the presence of aqueous amines or ammonia, affording primarily the 17- esterified product. Under precisely the same conditions, 11-hydroxy-17α,21-orthodiesters are recovered unchanged from the reaction.

The compounds of the present invention were tested according to a modified McKenzie vasoconstriction test. Creams, prepared using the formulation given in Example 23, (at a concentration of 0.05% and dosage of 50 mg), were applied to the backs of twenty healthy volunteers. The occlusive tape, covering the sterile gauze used for the application, was removed after 16 hours and the areas viewed at time intervals up to six hours. The results of the test showed that, surprisingly beclomethasone 17,21-diacetate was of, at least, equal potency topically to both betamethasone 17-valerate and dexamethasone 17,21-dipropionate at the indicated dosage level. The other previously unknown steroids tested also showed good topical activity in this test.

The products of the present invention when mixed with pharmaceutically acceptable excipients and diluents, well known to those skilled in the art, are active in locally-applied topical formulations. Typical of these formulations are creams, ointments, lotions, eye-drops and oral inhalation sprays. The content of the active principle depends on the actual formulation, but are generally between 0.001% w/w and 0.5% w/w, more preferably between 0.01% w/w and 0.25% w/w.

The formulations prepared with the products of the present invention can be used in the topical management of corticosteroid-responsive dermatoses, which may include

Psoriasis

Eczemas

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Neurodermatitis
Seborrhoeic dermatitis
Contact dermatitis
Atopic dermatitis
Intertrigo

In addition, the 21-desoxybetamethasone 17-heptanoate prepared in Example 2 is especially suitable for use as a long-acting active principle in an intramuscular injection.

The following examples serve to illustrate the present invention, without in any way limiting the scope thereof.

EXAMPLE 1 : PREPARATION OF BETAMETHASONE 11-TRIFLUOROACETATE 17-VALERATE 21-ACETATE

Four experiments were carried out to illustrate the fact that the acylation conditions of the present invention are faster than those of the prior art. The first experiment used the conditions of British Patent 1.097.164, Example 4, whilst the second used twice the amount of starting betamethasone 11-trifluoroacetate 21-acetate as was present in the first experiment. The other two trials used conditions from the present invention. Samples were removed at timed intervals and diluted with water, then chloroform extracted, which was washed with water and dried by passage through anhydrous sodium sulphate. The course of each reaction was monitored by thin layer chromatography, and the results are given in Table I. These clearly indicated that the reaction is complete in a shorter time with considerably less reagents present when the process of the present invention is employed.

EXAMPLE 2 : PREPARATION OF 21-DESOXYBETAMETHASONE 17-HEPTANOATE

Heptanoic anhydride (8.40 ml; 31.78 mmoles) and trichloroacetic acid (5.20 g; 31.82 mmoles) were mixed at 0°C, after which p-toluenesulphonic acid (0.50 g) and 9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (10.00 g; 21.16 mmoles) were added. The mixture was stirred at 40-45°C for 4 hours, cooled to ambient temperature, and then poured into 50% aqueous isopropylamine. The precipitated solid was filtered, well washed with water, and dried at 50°C to give 9.48 g of 21-desoxybetamethasone 17-heptanoate. Recrystallisation from methanol gave an analytically pure material, with the following characteristics: melting point 194-6°C and specific rotation in dioxan +54.28°.

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EXAMPLE 3 : PREPARATION OF DEXAMETHASONE 17-VALERATE 21-ACETATE

Valeric anhydride (3.90 ml; 19.47 mmoles) was added to previously cooled trifluoroacetic acid (1.50 ml; 19.60 mmoles), followed by benzenesulphonic acid (250 mg) and finally 9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 21-acetate (5.00 g; 9.68 mmoles). The mixture was stirred at 40-45°C for two hours, before 25% ammonium hydroxide was added. After stirring for 30 minutes, the mixture was poured into ice cold water and the precipitated solid collected by filtration, washed with water and dried at 50°C. The product, which weighed 4.80 g, was shown to be chromatographically identical with an authentical sample of the title compound. Recrystallisation gave a product with a melting point of 159°C.

EXAMPLE 4 : PREPARATION OF BECLOMETHASONE 17α,21-DIACETATE

Acetic anhydride (2.00 ml; 21.16 mmoles), trifluoroacetic acid (2.00 ml; 26.13 mmoles) and p-toluenesulphonic acid (0.25 g) were mixed at 0°C, and 9α-chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (2.50 g; 4.95 mmoles) was added. The mixture was stirred at 40°C for 1 hour 35 minutes, then cooled to 0°C and tetrahydrofuran (10 ml) and 12.5% aqueous ammonia (25 ml) added. After stirring for 30 minutes, the mixture was poured into ice cold water. The precipitated product was filtered, washed with water, dried at 50°C to yield 2.27 g of the above compound. An analytical sample was obtained by recrystallisation from methanol and had the following analytical values: melting point 228-231°C and specific rotation in chloroform of +87.28°.

EXAMPLE 5 : PREPARATION OF 9α,11β-DICHLORO-17α,21-DIHYDROXY-16β-METHYLPREGNA-1,4-DIENE-3,20-DIONE 17-VALERATE 21-ACETATE

Trifluoroacetic acid (4.80 ml; 62.72 mmoles), valeric anhydride (4.80 ml; 23.97 mmoles) and methanesulphonic acid (0.400 ml) were mixed at 0°C and then 9α,11β-dichloro-17α,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 21-acetate (7.50 g; 15.98 mmoles) was added. The mixture was stirred at 40°C for 2 hours, then poured slowly into ice cold water. Collection of the precipitate by filtration, washing with water and drying at 50°C yielded 8.90 g of the title compound. Recrystallisation from methanol gave an analytically pure sample with specific rotation in dioxan of +110.53°. The CI mass spectrum exhibits a typical molecular ion pattern centred on $m/_e$ 553 (M + 1), with the base peak at $m/_e$ 323.

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EXAMPLE 6 : PREPARATION OF 21-DESOXYBECLOMETHASONE 17-BUTYRATE

Butyric anhydride (5.25 ml; 32.19 mmoles), trifluoroacetic acid (5.25 ml; 68.60 mmoles) and methanesulphonic acid (0.45 ml) were mixed at 0°C, and then 9α-chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (7.50 g; 15.34 mmoles) was added. The reaction mixture was stirred at 40°C for 2 hours 30 minutes, and then poured into a mixture of tetrahydrofuran (17.4 ml) and 12.5% aqueous ammonia (43.5 ml). After stirring for 15 minutes, the mixture was poured into ice cold water, the product filtered, washed with water and dried at 50°C to yield 6.29 g of the title compound. After washing with an ice-cold methanol and acetone mixture, the product had the following analytical values : melting-point 250-252°C and specific rotation in chloroform +102.72°.

EXAMPLE 7 : PREPARATION OF 9α-CHLORO-17α-HYDROXY-16β-METHYLPREGNA-1,4-DIENE-3,11,20-TRIONE 17-BUTYRATE

The use of trifluoroacetic acid (3.50 ml; 45.73 mmoles), butyric anhydride (3.20 ml; 19.62 mmoles), methanesulphonic acid (0.25 ml) with 9α-chloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione (5.00 g; 12.79 mmoles) in the normal fashion at 40°C for 2 hours, yields, after precipitation in water and recrystallisation from methanol:dichloromethane:di-isopropyl ether, 5.27 g of the title compound. The melting point was 154-5°C and the specific rotation in chloroform was +198.83°.

EXAMPLE 8 : PREPARATION OF 9α,11β-DICHLORO-17α-HYDROXY-16β-METHYL-PREGNA-1,4-DIENE-3,20-DIONE 17-VALERATE

Valeric anhydride (4.80 ml; 23.97 mmoles) was added to cooled trifluoroacetic acid (4.80 ml; 62.72 mmoles) followed by methanesulphonic acid (0.400 ml) and finally 9α,11β-dichloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,20-dione (7.50 g; 18.23 mmoles).

The temperature was raised to 40°C and the mixture stirred for 1 hour 45 minutes, then poured slowly into ice cold water. The solid so obtained was filtered, washed with water, vacuum dried over potassium hydroxide pellets and immediately recrystallised from methanol to yield 6.97 g of the title compound. Further product could be obtained by concentration of the mother liquors. The melting point was 170-2°C and specific rotation in dioxan was +118.54°.

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EXAMPLE 9 : PREPARATION OF BETAMETHASONE 17-VALERATE 21-ACETATE

a) Trifluoroacetic acid (31.32 ml; 0.205 m les), valeric anhydride (41.04 ml; 0.409 moles) and p-toluenesulphonic acid (2.70 g) were mixed at 0°C and 9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 21-acetate (54.00 g; 0.102 moles) was then added. The temperature was raised to 40°C and the mixture stirred efficiently for 1 hour 25 minutes. Treatment with an ice-cold 10% pyridine : water mixture, followed by dissolution of the oily solid in methanol and precipitation in ice cold water gave a crystalline product, which was filtered, washed with water and dried at 50°C. The yield of betamethasone 11-trifluoroacetate 17-valerate 21-acetate was 60.10 g, the product having an $E^{1\%}_{1\ cm}$ in methanol of 242 at 235-7 nm.

b) The betamethasone 11-trifluoroacetate 17-valerate 21-acetate can then be transformed into betamethasone 17-valerate 21-acetate by the following general process:

The starting material was mixed with the chosen reagent in the solvent and stirred at the given temperature for the specified time. The product was obtained by precipitation in ice cold water, filtration, water washing, and drying at 50°C.

The results of various experiments are given in Table II.

EXAMPLE 10 : PREPARATION OF BETAMETHASONE 17-VALERATE

a) According to Portuguese Patent 71.309, Example 1, 9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 17-valerate 21-acetate (45.00 g) prepared as in Example 9a, methanesulphonic acid (2.25 ml) and absolute methanol (135 ml) were stirred, with the exclusion of moisture, for 45 hours at 18°C and then 23.5 hours at between 18°C and 25°C. The mixture was poured into ice cold water, and the precipitated solid filtered, well washed with water, dried at 50°C to yield 38.50 g of betamethasone 11-trifluoroacetate 17-valerate. Recrystallisation from hot aqueous methanol gave an analytical sample with a melting point of 174-177°C.

b) The betamethasone 11-trifluoroacetate 17-valerate can then be transformed into betamethasone 17-valerate by the following general process:

The starting material was mixed with the chosen reagent in absolute methanol and stirred at the given temperature for the specified time. The product was obtained by precipitation in ice cold water, filtration, water

.../...

TABLE II

Betamethasone 11-trifluoroacetate 17-valerate 21-acetate		Chosen Reagent	Reagent		Absolute Methanol ml	Water ml	Time minutes	Temperature °C	Yield g	Melting Point °C
g	mmoles		ml	mmoles						
2.00	3.25	Cyclohexylamine	0.05	0.44	12	-	15	22	1.55	204
2.00	3.25	Benzylamine	0.04	0.37	12	-	15	21	1.53	197-200
2.00	3.25	Diethylamine	0.05	0.48	12	-	20	23	1.55	202-208
1.00	1.63	Piperidine	0.002	0.02	6	-	2.5 days	28	0.78	204-205
5.00	8.13	Triethylamine	0.50	3.58	25	-	20	10	4.02	203-4
2.00	3.25	Ammonia in Absolute Methanol	6.8	2.33	5.2	-	30	21	1.56	203-4
2.00	3.25	Triethylamine	0.20	1.43	12	0.20	30	24	1.59	198-9

TABLE III

Betamethasone 11-trifluoroacetate 17-valerate		Chosen Reagent	Reagent		Absolute Methanol ml	Water ml	Time minutes	Temperature °C	Yield g	Melting Point °C
g	mmoles		ml	mmoles						
2.00	3.49	Ethylamine	0.05	0.76	12	-	20	25	1.60	183-8
2.00	3.49	Butylamine	0.04	0.40	12	-	20	22	1.59	186-8
2.00	3.49	Ethylenediamine	0.10	1.49	12	-	30	21	1.67	192
2.00	3.49	Morpholine	0.20	2.31	12	-	20	21	1.56	193-4
2.00	3.49	Pyrrolidine	0.05	0.60	12	-	20	22	1.60	185-7
2.00	3.49	Triethanolamine	0.04	0.30	12	-	30	21	1.57	193
2.00	3.49	Ammonia in Absolute Methanol	6.8	2.33	5.2	-	20	22	1.53	192-4
2.00	3.49	Ammonium Hydroxide	0.10	1.47	12	-	15	28	1.65	196
2.00	3.49	Isopropylamine	0.10	1.17	12	0.10	15	28	1.70	189-91

washing and drying at 50°C.

The results of various experiments are given in Table III.

EXAMPLE 11 : PREPARATION OF 9α-FLUORO-11β,17α-DIHYDROXY-21,21-DI-IODO-16β-METHYLPREGNA-1,4-DIENE-3,20-DIONE 17-VALERATE

a) Valeric anhydride (15.03 ml; 75.05 mmoles) and trifluoroacetic acid (13.20 ml; 172.48 mmoles) were mixed at 0°C, then methanesulphonic acid (1.25 ml) followed by 9α-fluoro-11β,17α-dihydroxy-21,21-di-iodo-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (25.00 g; 34.52 mmoles) were added. After stirring for two hours, the reaction mixture was poured slowly into a 0.025M disodium hydrogen phosphate solution. The aqueous phase was decanted off, and the residue dissolved in 50% acetone : methanol. After precipitation in ice cold water, the product was filtered, washed well with water, and dried at 35°C to yield 27.55 g. An analytical sample of this unstable product was obtained from aqueous methanol in the presence of a small amount of p-toluenesulphonic acid. The iodine content was found to be 28.5%.

b) The above product (3.00 g) was dissolved in methanol (18 ml) and triethylamine (3 ml; 21.54 mmoles) was added, after which the mixture was stirred for 30 minutes at room temperature. Precipitation in ice cold water yielded the title compound, which was filtered, washed with water and dried at 35°C. The iodine content was shown to be 23.7%.

EXAMPLE 12 : PREPARATION OF 21-DESOXYBETAMETHASONE 17-VALERATE

a) Trichloroacetic acid (2.60 g; 15.91 mmoles) and valeric anhydride (3.18 ml; 15.88 mmoles) were mixed at 0°C, then p-toluenesulphonic acid (250 mg) was added, followed by 9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (5.00 g; 10.58 mmoles). The mixture was warmed to 40°C and maintained at this temperature for 4 hours. After cooling to ambient temperature, triethylamine (25 ml) was added and stirring continued for a further 30 minutes. Precipitation with ice cold water gave a solid, which was filtered, washed with water and dried at 50°C. Recrystallisation from methanol gave an analytical sample with a melting point of 216-8°C, and a rotation in dioxan of +62.17°.

b) When the reaction above is not treated with triethylamine, but merely precipitated in water, 21-desoxybetamethasone 11-trifluoroacetate 17-valerate is obtained.

.../...

c) 9α-Fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 17-valerate (2.00 g; 3.59 mmoles) in absolute methanol (24 ml) was treated with 100% hydrazine (0.400 ml; 12.52 mmoles) for 15 minutes at 24°C. The reaction mixture was poured into ice cold water, and the product filtered, washed and dried to yield 1.56 g of the title compound, having a melting point of 212-5°C.

EXAMPLE 13 : PREPARATION OF DEXAMETHASONE 17,21-DIPROPIONATE

Trifluoroacetic acid (2.11 ml; 27.57 mmoles) was cooled to 0°C, and propionic anhydride (2.37 ml; 18.39 mmoles) was added, followed by methanesulphonic acid (0.25 ml) and 9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 21-propionate (5.00 g; 9.18 mmoles). After stirring at 40-45°C for 1 hour, the mixture was poured into a 50% aqueous solution of diethylamine. Filtration, washing and drying at 50°C gave 4.10 g of dexamethasone 17,21-dipropionate, with a melting point of 204-6°C. This melting point was unchanged on recrystallisation from aqueous methanol.

EXAMPLE 14 : PREPARATION OF BECLOMETHASONE 17-ACETATE

a) Triethylamine (0.200 ml; 1.43 mmoles) was added to a solution of 9α-chloro-11β-hydroxy-16β-methyl-17α,21(1'-methyl-1'-methoxy)methylenedioxy-pregna-1,4-diene-3,20-dione 11-trifluoroacetate (2.00 g; 3.56 mmoles) in methanol (8 ml), tetrahydrofuran (8 ml) and water (2 ml). After stirring overnight the mixture was poured into ice cold water, the product filtered, washed with water and dried at 50°C to yield 1.50 g of the title product. Recrystallisation from methanol gave a compound with a melting point of 221-223°C and a specific rotation in dioxan of +106.36°.

b) When the reaction mixture in Example 4 was precipitated in water, without prior treatment with ammonia, beclomethasone 11-trifluoroacetate 17,21-diacetate was obtained. This was reacted with anhydrous methanesulphonic acid in absolute methanol, by the process given in Portuguese Patent 71.039, to yield beclomethasone 11-trifluoroacetate 17-acetate, which was further treated with an amine to give beclomethasone 17-acetate. Recrystallisation from methanol gave an analytical sample with a specific rotation in dioxan of +106.58°.

.../...

EXAMPLE 15 : PREPARATION OF BECLOMETHASONE 17,21-DIPROPIONATE

a) Trifluoroacetic acid (1.20 ml; 15.68 mmoles) was cooled to 0°C, when propionic anhydride (1.512 ml; 11.73 mmoles) was added, followed by methanesulphonic acid (0.20 ml) and 9α-chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 21-propionate (4.00 g; 7.13 mmoles). The mixture was heated to 80°C and maintained at this temperature for 2.5 hours, with stirring. After precipitation with ice cold water, the product was filtered, washed well with water, and dried at 50°C to yield 4.02 g of beclomethasone 11-trifluoroacetate 17,21-dipropionate. Recrystallisation from methanol gave an analytically pure sample with a melting point of 176-7°C.

b) 9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate 17,21-dipropionate (3.00 g; 4.86 mmoles) was dissolved in methanol (18 ml) and dioxan (12 ml), after which morpholine (0.300 ml; 3.48 mmoles) was added. After stirring at 25°C for 1 hour, the reaction mixture was neutralised with 50% aqueous acetic acid, and precipitated in ice cold water. Filtration, washing with water and drying at 50°C gave 2.45 g of beclomethasone dipropionate 17,21-dipropionate. After a recrystallisation from acetone, the product complied with the United States Pharmacopoeia XX h.p.l.c. assay for this product.

EXAMPLE 16 : PREPARATION OF 21-DESOXYBECLOMETHASONE 17-VALERATE

a) A mixture of trifluoroacetic acid (27.00 ml; 353 mmoles) and valeric anhydride (13.50 ml; 67.4 mmoles) was prepared at 0°C, after which p-toluene sulphonic acid (1.80 g) and 9α-chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (18.00 g; 36.8 mmoles) were added. The temperature was raised to 40°C and the reaction stirred for 2 hours. Precipitation with ice cold water gave an oily solid, which crystallised when triturated with methanol. Filtration and drying at 50°C gave 17.71 g of 21-desoxybeclomethasone 11-trifluoroacetate 17-valerate, with a melting point of 187-90°C.

b) The above product was then transformed into 21-desoxybeclomethasone 17-valerate by the following procedure:

The starting material was mixed with the chosen reagent in the solvent and stirred at the given temperature for the specified time. The product was obtained by precipitation in ice cold water, filtration, water wash

.../...

TABLE IV

21-Desoxybeclomethasone 11-trifluoroacetate 17-valerate		Chosen Reagent	Reagent		Absolute Methanol ml	Water ml	Time minutes	Temperature °C	Yield g	Melting Point °C
g	mmoles		ml	mmoles						
2.00	3.49	Butylamine	0.04	0.40	12	-	15	21	1.62	239-41
2.00	3.49	Diethylamine	0.10	0.97	12	-	15	21	1.61	239-40
2.00	3.49	Triethylamine	0.2	1.43	12	-	120	21	1.60	240-42
2.00	3.49	Pyrrolidine	0.20	2.40	12	0.2	15	21	1.60	240

ing and drying at 50°C.

The results f some experiments are given in Table IV.

EXAMPLE 17 : PREPARATION OF CLOBETASOL 17-PROPIONATE

a) Trifluoroacetic acid (2.23 ml; 29.14 mmoles) and propionic anhydride (2.50 ml; 19.40 mmoles) were mixed at 0°C, after which 70% perchloric acid (0.272 ml) and 21-chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 11-trifluoroacetate (4.90 g; 9.67 mmoles) were added. Stirring at 40-45°C for 3 hours and precipitation in ice cold water, gave a solid, which was filtered, washed well with water and dried at 50°C. The product, clobetasol 11-trifluoroacetate 17-propionate, weighed 5.15 g.

b) The product obtained above (4.78 g) was suspended in methanol (28.7 ml) and triehtylamine (1.195 ml; 8.58 mmoles) was added. The mixture was stirred at 25°C for 30 minutes and then neutralised by the addition of 50% aqueous acetic acid. After precipitation, the product was filtered, washed and dried at 50°C to yield 3.72 g. An analytical sample of the clobetasol propionate was obtained by recrystallisation from methanol and had a melting point of 200°C and specific rotation in dioxane of +99.21°.

c) The product obtained in stage a) above (100 mg; 0.18 mmoles) was suspended in absolute methanol. After adding 100% hydrazine (100 µl; 0.62 mmoles), the mixture was stirred at 28°C for 15 minutes, and then precipitated in ice cold water. The product was shown to be chromatographically identical with that obtained in stage b) above.

EXAMPLE 18 : PREPARATION OF CLOBETASONE 17-BUTYRATE

Butyric anhydride (5.28 ml; 32.37 mmoles), trifluoroacetic acid (2.376 ml; 31.05 mmoles) were mixed at 0°C, then methanesulphonic acid (0.200 ml), nitromethane (20.0 ml) and 21-chloro-9α-fluoro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione (4.00 g; 10.23 mmoles) were added. The reaction was stirred at 40°C for 3 hours and then poured slowly into ice cold water, to give an oily solid, which was filtered, water washed and dried to yield 3.71 g. Recrystallisation from methanol gave an analytical sample with a melting point of 184-6°C and a specific rotation in dioxan of +127.98°.

EXAMPLE 19 : PREPARATION OF BETAMETHASONE 17-BENZOATE

.../...

9α-Fluoro-11β-hydroxy-16β-methyl-17α,21(1'-phenyl-1'-methoxy)methylenedioxy-pregna-1,4-diene-3,20-dione 11-trifluoroacetate (3.00 g; 5.04 mmoles) was dissolved in a mixture of methanol (12 ml), tetrahydrofuran (12 ml) and water (3 ml), then triethylamine (0.300 ml; 2.15 mmoles) was added. After stirring overnight, the product was obtained by precipitation in ice cold water, followed by filtration, washing and drying at 50°C. The yield of the title compound was 2.55 g. Recrystallisation from methanol gave an analytical pure sample with a melting point of 225°C and $E^{1\%}_{1\ cm}$ of 555 at 233-234 nm.

EXAMPLE 20 : PREPARATION OF PREDNISOLONE 17-VALERATE 21-ACETATE

a) Valeric anhydride (3.50 ml; 17.48 mmoles) was mixed with trifluoroacetic acid (2.30 ml; 30.05 mmoles) at 0°C, after which methanesulphonic acid (0.25 ml) and 11β,17α,21-trihydroxy-pregna-1,4-diene-3,20-dione 11-trifluoroacetate 21-acetate (5.00 g; 10.03 mmoles) were added. The reaction was warmed to 25°C, stirred for one hour, poured into ice cold water, to give an oily solid. This was dissolved in methanol and precipitated in water to give a solid, which was filtered, washed and dried, yielding 5.30 g of prednisolone 11-trifluoroacetate 17-valerate 21-acetate.

b) The above product (3.00 g; 5.15 mmoles) in absolute methanol (18 ml) was treated with triethylamine (2.40 ml; 17.21 mmoles) at 24°C for 5 hours. The product, which was obtained by precipitation in ice cold water, filtration, washing and drying, weighed 2.35 g, and had an $E^{1\%}_{1\ cm}$ of 279 at 241-3 nm in methanol.

EXAMPLE 21 : PREPARATION OF 9α-CHLORO-11β,17α,21-TRIHYDROXY-16β-METHYLPREGN-4-ENE-3,20-DIONE 17,21-DIPROPIONATE

The above product was prepared from 9α-chloro-11β,17α,21-trihydroxy-16β-methylpregn-4-ene-3,20-dione 11-trifluoroacetate 21-propionate by the method given for beclomethasone 17,21-dipropionate under Example 5.

EXAMPLE 22 : PREPARATION OF 6α-METHYLPREDNISOLONE 17-BUTYRATE 21-ACETATE

This was prepared in an analogous manner to that of 21-desoxybetamethasone 17-butyrate in Example 6, starting from 6α-methylprednisolone 11-trifluoroacetate 21-acetate.

.../...

EXAMPLE 23 : WATER MISCIBLE CREAM FORMULATION

A water miscible cream of clobetasol 17-propionate can be prepared as follows:

Part I - The following are mixed and melted at 70°C:

Cetostearyl alcohol ("Lanette O" R)	18.0%
Cetostearyl alcohol containing approximately 12 moles of ethylene oxide ("Eumulgin B1" R)	1.5%
Cetostearyl alcohol containing approximately 20 moles of ethylene oxide ("Eumulgin B2" R)	1.5%
Caprylic/capric acid triglyceride ("Myritol 318")	10.0%

Part II - Suspend at room temperature:

Clobetasol 17-propionate	the equivalent to 0.05% of clobetasol
Glycerol	5.0%

and ball mill it.

Part III - Dissolve at boiling point:

Methyl 4-hydroxybenzoate	0.3%
in	
Bidistilled water	63.65%

Cool to 70°C and adjust volume, if necessary.

One third of Part III is added to Part I with stirring at 70°C, then Part II is added, followed by the remainder of Part III at 70°C. The mixture is cooled slowly with stirring, when a jelly begins to set at about 55°C. The stirring is continued until ambient temperature to ensure good homogeneity. Th pH will be between 5.0 and 5.3.

EXAMPLE 24 : LOTION FORMULATION

A lotion formulation of 9,11-dichloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-valerate can be prepared as follows:

.../...

Part I - The following are mixed and melted at 70°C:

Cetostearyl alcohol ("Lanette O" R)	0.65%
Ethyleneglycol stearate ("Cutina AGS" R)	0.65%
Cetostearyl alcohol containing approximately 20 moles of ethylene oxide ("Eumulgin B2" R)	0.93%
Liquid paraffin	1.95%

Part II - Suspend at room temperature:

9,11-Dichloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-valerate	the equivalent to 0.1% of the parent steroid
Glycerol B.P.	2.50%
Propan-2-ol	6.50%

and ball mill it.

Part III - Dissolve at boiling point:

Methyl 4-hydroxybenzoate	0.15%
in	
Glycerol B.P.	2.50%
Bidistilled water	84.05%

Cool to 70°C and adjust volume, if necessary.

Part III is added to Part I with stirring at 70°C, then Part II is added. The mixture is cooled with efficient stirring to ensure homogeneity.

EXAMPLE 25 : OINTMENT FORMULATION

An ointment of dexamethasone 17,21-dipropionate can be prepared as follows:

Solid vaseline	91.8%
Liquid paraffin	8.1%
Dexamethasone 17,21-dipropionate	the equivalent to 0.1% of dexamethasone

.../...

The vaseline is melted and maintained at 50°C with efficient stirring, whilst a ball-milled suspension of the dexamethasone 17,21-dipropionate in the liquid paraffin is added. The tubes are filled whilst the mixture is still hot and liquid.

EXAMPLE 26 : ORAL INHALATION SPRAY FORMULATION

A spray formulation of beclomethasone 17,21-diacetate can be prepared as follows:

Beclomethasone 17,21-diacetate (micronised)	12.06 mg
Linoleic acid	10.00 mg
Fluorotrichloromethane	9990.00 mg
Dichlorodifluoromethane	15000.00 mg

The linoleic acid is efficiently mixed with cold fluorotrichloromethane, then the micronised steroid is added. The mixing is continued until a completely uniform mixture is obtained. An evaporated fluorotrichloromethane must be replaced as necessary. Each inhaler is filled with the required amount, after which, the valves are attached, and the required dichlorodifluoromethane pumped in.

EXAMPLE 27 : INTRAMUSCULAR INJECTION FORMULATION

An intramuscular injection formulation of 21-desoxybetamethasone 17-heptanoate can be prepared as follows:

21-Desoxybetamethasone 17-heptanoate	1.298 g
Sesame oil	100 ml

The sterile micronised steroid is efficiently mixed with the sterile sesame oil to ensure a uniform mixture. Each ampoule is filled with 1 ml.

.../...

Certain compounds which can be made by the process of the invention are novel per se and form a further aspect of the present invention. These include:

9α-Fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-heptanoate;

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate;

9α,11β-Dichloro-17α,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-valerate 21-acetate;

9α-Chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-butyrate;

9α-Chloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione 17-butyrate;

9α,11β-Dichloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-valerate;

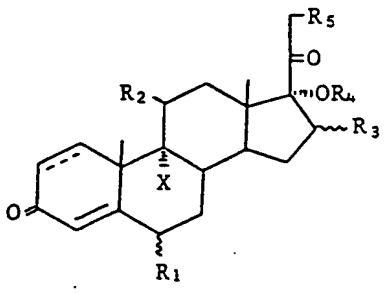
9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-acetate;

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregn-4-ene-3,20-dione 17,21-dipropionate.

The invention further includes pharmaceutical compositions which comprises a novel compound of the invention or a compound made by the process of the invention, and an inert pharmaceutically acceptable carrier therefor.

CLAIMS:

1. A process for the preparation of corticosteroid esters of the formula



(I)

wherein

---- signifies that a double bond can be present;

X is hydrogen, fluorine or chlorine;

R_1 is hydrogen, fluorine, chlorine or methyl, which may be either α or β;

R_2 is halogen, oxo, i.e. ketonic oxygen, or hydroxyl;

R_3 is hydrogen, α-methyl or β-methyl;

R_4 is an acyl group of the formula RCO, in which R is one of the following:

i) an alkyl group containing 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;

ii) an aralkyl group of 7 to 8 carbon atoms; or

iii) a phenyl group;

R_5 is hydroxyl or R_6; where

R_6 is hydrogen, halogen, two halogen atom substituents or OR_7, where R_7 is an acyl group of the formula R'CO in which R', which can be identical or different to R in the same molecule, is one of the following:

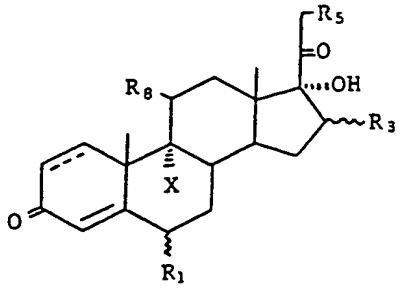
i) an alkyl group containing 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;

ii) an aralkyl group of 7 to 8 carbon atoms; or

iii) a phenyl group;

which comprises esterifying a compound of the formula

.../...

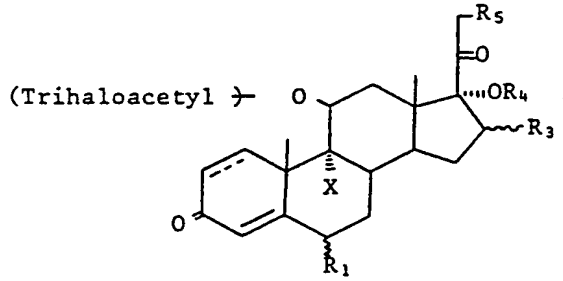


(III)

wherein X, R_1, R_3 and R_5 are as defined above, and

R_8 is trihaloacetate, halogen or oxo;

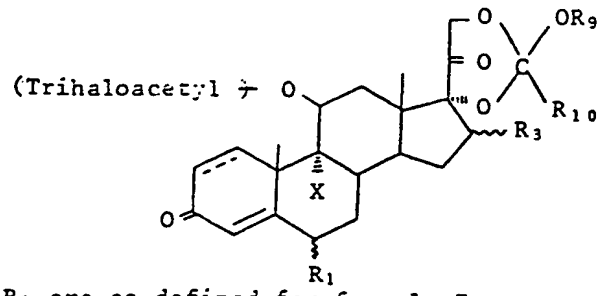
at the 17- position only, or at the 17- and 21- positions when R_5, in formula III, is hydroxyl, the said esterification being carried out with the anhydride of the acid containing the group it is desired to enter at the 17- position, or at the 17- and 21- positions, together with a pair of strong acids; and if desired eliminating immediately thereafter any 11-trihaloacetate substituent, to form a compound of formula I, wherein R_2 is hydroxyl, R_5 is R_6, and X, R_1, R_3 and R_4 are as defined above; or when R_8 is halogen or oxo and R_5 is R_6, isolating a compound of formula I after the said esterification; or treating a compound of formula IV from the esterification



(IV)

wherein R_5 is R_6, by eliminating the 11-trifluoroacetate group therefrom by reaction, in the presence of a lower alcohol, with an organic amine (other than one in which the nitrogen forms part of an aromatic ring), or ammonia gas dissolved in a suitable anhydrous solvent, or ammonium hydroxide or hydrazine, to produce a compound of formula I wherein R_2 is hydroxyl, R_5 is R_6 and X, R_1, R_3 and R_4 are as defined from formula I; or by so eliminating the 11-trihaloacetate group from a compound of formula

.../...



(V)

wherein X, R_1 and R_3 are as defined for formula I;

R_9 is an alkyl group of 1 to 3 carbon atoms; and

R_{10} is a hydrocarbon group comprising one of the following:

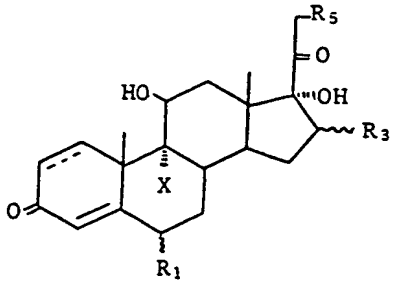
i) an alkyl group of 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;

ii) an aralkyl group of 7 to 8 carbon atoms; or

iii) a phenyl group;

to form a compound of formula I, wherein R_2 and R_5 are both hydroxyls and R_1, R_3, R_4 and X are as defined for formula I.

2. A process according to claim 1, wherein the compound of the formula III, in which R_8 is trihaloacetate, is prepared by the 11-trihaloacetylation of a compound of the formula



(II)

wherein X, R_1, R_3 and R_5 are as defined for formula I.

3. A process according to claims 1 or 2, wherein the trihaloacetate group is trifluoroacetate.

4. A process according to any preceding claim, wherein at least 1.5 moles of the acid anhydride is used, for each mole of the steroid to be esterified.

5. A process according to any preceding claim, wherein the pair of strong acids is chosen from a trihaloacetic acid plus one of the following:

.../...

p-toluenesulphonic acid, methanesulphonic acid, benzenesulphonic acid, perchloric acid, hydrochloric acid.

6. A process according to claim 5, wherein the trihaloacetic acid is trifluoroacetic acid or trichloroacetic acid.

7. A process according to claim 5 or 6, wherein at least 1.5 moles of the trihaloacetic acid is used, for each mole of the steroid to be esterified, and the second acid of the pair is present in at least a catalytic quantity.

8. A process according to any preceding claim, wherein, after said esterification of a compound of formula III, any 11-trifluoroacetate group is immediately eliminated by one of the following processes:

a) Treatment with an organic amine, other than an amine in which the nitrogen forms part of an aromatic ring, followed by precipitation in water;

b) Treatment with a mixture of an organic amine, as defined in a) above, and of water; or

c) Treatment with ammonium hydroxide solution.

9. A process according to any of the claims 1 to 8, wherein the amine used to remove the 11-trihaloacetate group is a primary amine, such as ethylamine, cyclohexylamine, isopropylamine, n-butylamine, benzylamine or ethanolamine.

10. A process according to any of the claims 1 to 8, wherein the amine used to remove the 11-trihaloacetate group is a secondary amine, such as diethylamine, diphenylamine, morpholine, piperidine or pyrolidine.

11. A process according to any of the claims 1 to 8, wherein the amine used to remove the 11-trihaloacetate group is a tertiary amine, such as triethylamine, triethanolamine or ethyldiisopropylamine.

12. A process according to any of the claims 1 to 8, wherein the anhydrous ammonia used to remove the 11-trihaloacetate group is dissolved in an anhydrous lower alcohol.

13. A process according to claim 12, wherein the lower alcohol is methanol or ethanol.

14. A process according to any of the claims 1 to 13, wherein the amine, anhydrous ammonia, ammonium hydroxide solution or hydrazine used to

.../...

remove the 11-trihaloacetate group is present in an amount from [illegible] a slight stoichiometric excess.

15. The compounds:

9α-Fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] noate;

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] diacetate;

9α,11β-Dichloro-17α,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] valerate 21-acetate;

9α-Chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] te;

9α-Chloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione [illegible]

9α,11β-Dichloro-17α-hydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] te;

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione [illegible] acetate;

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregn-4-ene-3,20-dione [illegible] prionate.

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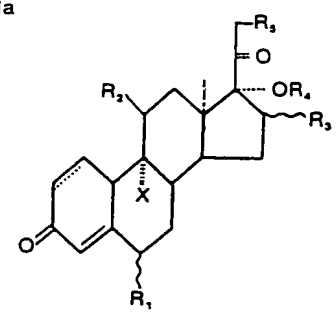
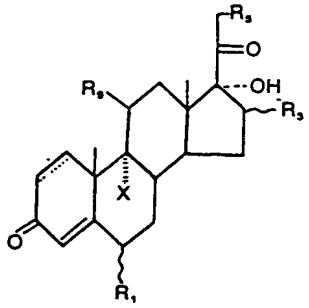
(54) **Steroidal esters and process for the preparation of steroidal esters.**

(57) A process for the preparation of corticosteroid esters of the formula



(I)

wherein
— signifies that a double bond can be present;
X is hydrogen, fluorine or chlorine;
R_1 is hydrogen, fluorine, chlorine or methyl, which may b either α or β;
R_2 is halogen oxo, i.e. ketonic oxygen, or hydroxyl;
R_3 is hydrogen, α-methyl or β-methyl;
R_4 is an acyl group
R_5 is hydroxyl or R_6; where
R_6 is hydrogen, halogen, two halogen atom substituents or OR_7, where R_7 is an acyl group
which comprises esterifying a compound of the formula



(III)

wherein X, R_1, R_2 and R_3 are as defined above, and
R_5 is trihaloacetate, ahlogen or oxo;
at the 17-position only, or at the 17- and 21-positions when R_5, in formula III, is hydroxyl the said esterification being carried out with the anhydride of the acid containing the group it is desired to enter at the 17-position, or at the 17- and 21-positions, together with a pair of strong acids; and if desired eliminating immediately thereafter any 11-trihaloacetate substituent, to form a compound of formula I, wherein R_2 is hydroxyl, R_5 is R_6, and X, R_1, R_3 and R_4 are as

(Continuation next page)

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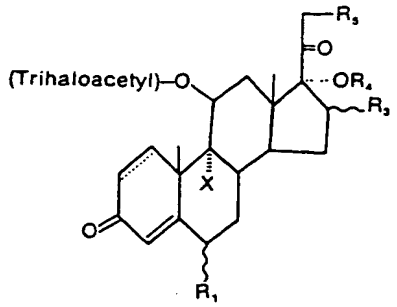
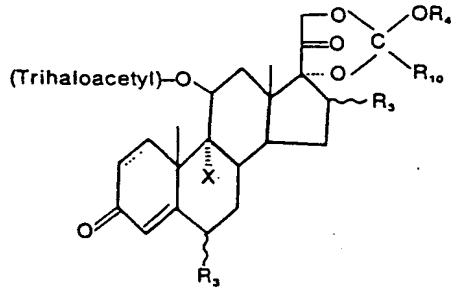
defined above; or when R_3 is halogen or oxo and R_5 is R_6, isolating a compound of formula I after the said esterification; or treating a compound of formula IV from the esterification



(IV)

wherein R_5 is R_6, by eliminating the 11-trihaloazetate group therefrom by reaction, in the presence of a lower alcohol, with an organic amine (other than one in which the nitrogen forms part of an aromatic ring), or ammonia gas dissolved in a suitable anhydrous solvent, or ammonium hydroxide or hydrazine, to produce a compound of formula I wherein R_2 is hydroxyl, R_5 is R_6 and X, R_1, R_3 and R_4 are as defined from formula I; or by so eliminating the 11-trihaloacetate group from a compound of formula



(V)

wherein X, R_1 and R_3 are as defined for formula I.

European Patent Office

EUROPEAN SEARCH REPORT

Application number 0072200

EP 82 30 4116

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
D,A	GB - A - 1 097 165 (SCHERICO LTD.) * claims * --	1-3,8	C 07 J 5/00 7/00 A 61 K 31/57
D,A	GB - A - 1 097 164 (SCHERICO LTD.) * claims * --	1-3,8	
D,A	US - A - 4 024 131 (JAO EMERICO. VILLAX) * claims 19-22; columns 4,5 * --	1-3,8	
A	GB - A - 2 079 754 (PLURI CHEMIE ANSTALT) * claims * --	1-3,8	TECHNICAL FIELDS SEARCHED (Int. Cl. ³)
D	& PT - A - 71 309 --		C 07 J 5/00 7/00
A	US - A - 2 800 489 (TADEUS REICHSTEIN) * the whole document * --------	1-3,8	

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
The Hague	26-10-1982	HENRY

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

☒ LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

1. claims 1-15; Preparation of compounds of formula I starting from compounds of formula III.
2. claims 1,8-14; Preparation of compounds of formula I starting from compounds of formula V.

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:

☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims: 1-15